

100070.805

Fresenius D3

(19)



Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number:

0 022 922
A1

(12)

EUROPEAN PATENT APPLICATION

(21) Application number: 80103136.0

(51) Int. Cl. 3: A 61 M 1/03

(22) Date of filing: 06.06.80

(30) Priority: 24.07.79 DE 2929871

(43) Date of publication of application:
28.01.81 Bulletin 81/4

(54) Designated Contracting States:
AT BE CH DE FR GB IT LI LU NL SE

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(54) Aqueous concentrate for dialysis solutions.

(57) In order to obtain storable and bacteriostatic concentrates for dialysis solutions having, if any, small contents of acetate, the concentrates according to the invention are divided to two containers one of which contains an aqueous solution (A) of sodium carbonate or bicarbonate and the other of which contains an aqueous solution (B) of an acid forming physiologically compatible sodium and calcium salts as well as calcium cations and optionally magnesium cations, whereby both solutions (A) and (B) may contain additionally sodium chloride and, if desired, potassium cations.

EP 0 022 922 A1

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4. Juni 1980
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Aqueous Concentrate For
Dialysis Solutions

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Priority: German Patent Application
P 29 29 871.3 filed on July 24, 1979

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It is known to use haemo dialysis solutions which contain sodium bicarbonate together with sodium chloride and optionally other alkali and alkali earth chlorides. But there has been found as
20 disadvantage of such dialysis solutions containing bicarbonate that calcium and magnesium carbonates may precipitate. In order to avoid these disadvantages, different methods have been used.

1 One method was to replace sodium acetate for the bicarbonate
since the alkali earth acetates are easily soluble, so that
no precipitates of slightly soluble calcium or magnesium
compounds result. But since the acetate is partly trans-
5 ferred into the blood, sometimes the patients show acidosis
which makes undesirable the use of acetate instead of bi-
carbonate in haemo dialysis solutions. Another method was
that, to bubble carbon dioxide into the dialysis solution
in order to maintain the pH value of the dialysis solution
10 in the acidic range and to suppress the formation of
slightly soluble magnesium and calcium carbonates. But
bubbling carbon dioxide into a dialysis solution is a
process complicated and capable of interferences, and in
this method the introduced amount of carbon dioxide and
15 thus the pH value can be controlled only relatively bad.

Additionally the physicians prefer storable concentrates
for dialysis solutions which concentrates have only to be
diluted by water to become useful. But concentrates of
20 aqueous sodium bicarbonate solutions containing calcium
ions are not stable and only slightly bacteriostatic.

The object of the invention was to obtain concentrates for
dialysis solutions which are storable and bacteriostatic,
25 also in their final composition, and thus may be left
standing for some time without the necessity of bubbling
carbon dioxide into the solution. Moreover the dialysis
solutions shall contain at most slow amounts of acetate.

30 The inventive aqueous concentrate for dialysis solutions
containing sodium chloride, carbonate or hydrocarbonate,
respectively, calcium cations and optionally magnesium
and/or potassium cations is characterized in that it is
divided to two containers one of which contains an aqueous
35 solution (A) of sodium carbonate or bicarbonate and the
other of which contains an aqueous solution (B) of the
calcium cations and, if magnesium cations are contained,
of the magnesium cations, as well as of an acid which forms

- 1 physiologically compatible sodium, calcium and optionally
potassium and magnesium salts.

According to the first embodiment of the invention the
5 solution (A) contains sodium carbonate and the solution
(B) contains hydrochloric acid as the acid.

It is unusual to use strong acids such as hydrochloric
acid in physiological aqueous solutions. But the said
10 acid is immediately reacted when combined with the aqueous
solution containing the sodium carbonate, whereby sodium
chloride is formed. During that reaction the sodium car-
bonate forms the equivalent amount of sodium bicarbonate,
and in the event of a corresponding proportionation of the
15 amount of hydrochloric acid, a smaller part of the said
sodium bicarbonate is decomposed to form additional sodium
chloride and carbon dioxide which has the function of the
carbon dioxide which is usually bubbled into the solution
and adjusts the pH value of the dialysis solution.

20 Thus since the hydrochloric acid contained in the solution
(B) serves on the one hand completely to convert the
sodium carbonate to sodium bicarbonate and on the other
hand to decompose a smaller portion of the formed sodium
25 bicarbonate forming carbon dioxide, it is preferred that
the solution (B) contains 1.05 to 1.3, preferably 1.05 to
1.2 mole of HCl per mole of Na_2CO_3 in the solution (A).
One mole of the said hydrochloric acid is necessary to
convert quantitatively the sodium carbonate to sodium
30 bicarbonate, whereas the remaining amount of hydrochloric
acid serves to release CO_2 .

The amount of sodium chloride formed during the said
reactions may be calculated, so that there is added to
35 the solutions (A) and/or (B) the amount of sodium chloride
necessary for the dialysis solution, less the amount of
sodium chloride formed in the above reactions. The said
sodium chloride which is necessary in the dialysis solu-

tion to make it substantially isotonic with the blood liquid, may be added to each of the both solutions (A) and (B) or partially to both. Additionally there are added calcium chloride and optionally magnesium chloride and potassium chloride to the concentrate in the usual manner. The amounts of these compounds in the dialysis solutions are known and are not distinguished from the prior art. However, it is suitable to have in the solution (A) only sodium carbonate, but in the solution (B) additionally to the hydrochloric acid all other compounds, since then the solution (A) may be used as standard stock solution for solutions (B) having different concentration, if only the concentration of hydrochloric acid thereof is in conformity with the concentration of sodium carbonate in the solution (A) corresponding to the above statements.

Since smaller amounts of acetate are not dangerous, it is also possible to replace acetic acid for a smaller portion of the hydrochloric acid.

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For example per mole of sodium carbonate in the solution (A) 1 mole of HCl and 0,05 to 0,3 mole of acetic acid should be present in the solution (B).

25 According to a second embodiment of the invention the solution (A) contains sodium bicarbonate.

It is surprising that the sodium bicarbonate solutions designated as aqueous solution (A) are stable during long time storage and result in stable dialysis solutions without bubbling carbon dioxide into the solutions to stabilize them.

For this effect it is sufficient that only relatively small amounts of an acid which forms the stated physiologically compatible alkali and alkali earth salts are used. This results in the advantage for example in the event of the use of acetic acid, that the ready dialysis solution may

1 contain only small amounts of alkali acetate which do not
result in acidosis. Preferably the aqueous solution (B)
contains 0,01 to 0,25, especially 0,03 to 0,15, such as
for example about 0,05 mole of the stated acid per mole
5 of sodium bicarbonate in the aqueous solution (A).

By the combination of the two solutions (A) and (B) and
with dilution water the hydrogen ions react with a small
part of the sodium bicarbonate forming CO_2 which remains
10 in the dialysis solution and stabilizes it by avoiding a
formation of alkali earth carbonates and by adjusting the
pH value of the dialysis solution.

As acid in the aqueous solution (B) inorganic or organic
15 acids may be used, which form physiologically compatible
sodium and calcium salts and, if the aqueous concentrates
contain magnesium and potassium cations, form physiological-
ly compatible magnesium and potassium salts, too. Such acids
which may be used according to the invention are for example
20 acetic acid, citric acid, lactic acid, hydrochloric acid
and/or amino acids.

Acetic acid is preferred among the said acids, if sodium
bicarbonate is used in the solution (A). The said acetic
25 acid may be used without hesitation, since the amount
thereof is relatively small in comparison with the amount
of hydrocarbonate, so that from the dialysis solution only
neglectible amounts of acetate can be transferred into the
blood of the patient, so that no risk of acidosis exists.
30

The sodium chloride may be contained in both aqueous
solutions (A) and/or (B), but it is preferably present in
the solution (A) in a concentration as high as possible.
35 The sodium chloride increases the autosterility of the
aqueous solutions. If the aqueous solution (A) contains a
great portion of sodium cations, by different dosage of
the relative amount of the solution (A) at the combination
with the solution (B) and with dilution water, optional

1 millival values for the sodium in the dialysis solution
may be adjusted without having stock solutions of different
concentrations. That by the superdosage or underdosage
relating to the solution (A) also the other components,
5 such as sodium bicarbonate, are super or under dosed, is
no disadvantage, since the bicarbonate is rapidly decom-
posed by the body.

It may be suitable, if the aqueous solution (B) contains
10 additionally glucose. The amount of the glucose in the
solution (B) is suitably 5 to 400 gs/l, preferably 15 to
80 gs/l.

An increased storage stability of the concentrates according
15 to the invention is obtained, if the solution (A) is main-
tained in a container and under such conditions, that no
or only small escape of CO_2 from the solution and the
gaseous phase above the said solution out of the said
container is possible. This may be reached in a different
20 manner. For example the container can be manufactured of a
material or with such a thickness of the wall that no CO_2
or only a very small amount of CO_2 escapes from the
solution through the wall of the container. Another
suitable method is to store the solution (A) in comparably
25 big containers, so that the ratio of the volume to the
surface area of the liquid body is relatively great. There-
by the interface between the solution and the wall of the
container, where CO_2 may escape by diffusion, is relatively
small in comparison with the volume of the solution. This
30 is especially important, if for the storage of the solution
plastic containers must be used for which a diffusion of
 CO_2 through the wall of the container cannot be excluded.
It is surprising that by the choice of big storage con-
tainers the bicarbonate solution (A) remains completely
35 stable for long periods of time. The stability of the said
solution can still be improved by a storage at low tempera-
tures.

1 In a surprising manner the solutions are unstable, if they contain too much unbound CO_2 at the time of filling into the containers, since then the containers inflate. This is avoided by the invention.

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The aqueous concentrates for dialysis solutions according to the invention have several important advantages over known concentrates for the same purpose. A first advantage is that the solutions are completely stable at the storage
10 during a long period of time as well as at a longer storage during the use without the precipitation of slightly soluble alkali earth compounds and without turbidity.

15 Another advantage is that by the concentrates according to the invention dialysis solutions are obtained which do not result in any physiological disadvantage, such as acidosis.

Finally a high autosterility and a good flexibility of the
20 dosage are obtained, so that optional sodium concentrations in the dialysis solution may be adjusted without having stock solutions of different concentration.

In the practical use both aqueous solutions (A) and (B) are
25 mixed together and with the dilution water separately from the dialysis device or within the dialysis device immediately before the membrane, whereby suitably the solution (A) is diluted with water and then the solution (B) is metered. This may be done suitably by forced dosage in order to
30 adjust the correct ratio of both solutions (A) and (B), whereby in the mixing device the solution obtains the necessary temperature. Moreover as safety precaution a conductivity and optionally a pH value, density- and/or flow control device may be provided. If desired, the feed
35 of the solutions (A) and/or (B) may be made dependent from the above mentioned measured values, and by these measurements the feed may be controlled.

1 Example 1

Solution (A):

5 water 1 l

NaHCO₃ 132,3 gs (1575 mmole)

sodium chloride 61,36 gs (1050 mmole)

filling up with water to a total volume of 2 l

10 Solution (B):

Water 0,5 l

acetic acid 10,517 gs (175 mmole)

NaCl 122,72 gs (2100 mmole)

15 KCl 5,227 gs (70 mmole)

MgCl₂·6H₂O 7,116 gs (35 mmole)CaCl₂·6H₂O 13,42 gs (61,25 mmole)

filling up with water to a total volume of 1 l

20 During the combination of both aqueous solutions there has been diluted with 32 l of water to totally 35 l of dialysis solution. This solution contained 5 mmole CO₂, and in a surprising manner this amount was sufficient to maintain the dialysis solution stable during storage for a longer

25 time, too.

Example 2

Solution (A):

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Water 1000 l

Na₂CO₃ water-free 211,47 kg

filling up with water to a total volume of 1500 l

35 Solution (B):

water 750 l

NaCl 181,0 kg

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1 HCl, 37%ig, 212,1 kg

MgCl₂.6H₂O 10,674 kg

CaCl₂.6H₂O 20,13 kg

filling up with water to a total volume of 1500 l

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1 Patent Claims

1. An aqueous concentrate for dialysis solutions containing sodium chloride, carbonate or hydrocarbonate anions
5 respectively, calcium cations and optionally magnesium and/or potassium cations, characterized in that it is divided to two containers one of which contains an aqueous solution (A) of sodium carbonate or bicarbonate and the other of which contains an aqueous solution (B)
10 of an acid which forms physiologically compatible sodium, calcium and optionally potassium and magnesium salts, of the calcium cations and, if magnesium cations are contained, of the magnesium cations.
- 15 2. A concentrate according to claim 1, characterized in that it contains in the aqueous solution (A) sodium carbonate and in the aqueous solution (B) as acid hydrochloric acid.
- 20 3. A concentrate according to claim 2, characterized in that it contains in the solution (B) 1,05 to 1,3, preferably 1,05 to 1,2 mole HCl per mole Na_2CO_3 in the solution (A).
- 25 4. A concentrate according to claim 2 and 3, characterized in that it contains the sodium chloride and optionally the potassium chloride in the solution (A) and /or the solution (B).
- 30 5. A concentrate according to claims 2 through 4, characterized in that up to 0,3 mole-% of the HCl are replaced by acetic acid.
- 35 6. A concentrate according to claim 1, characterized in that it contains sodium bicarbonate in the aqueous solution (A).
7. A concentrate according to claim 6, characterized in

- 1 that it contains in the solution (B) 0,01 to 0,25,
preferably 0,03 to 0,15 mole of the acid per mole of
sodium bicarbonate in the solution (A).
- 5 8. A concentrate according to claim 6 and 7 characterized
in that it contains the sodium chloride and optionally
the potassium cations in the solution (A) in a concen-
tration as high as possible.
- 10 9. A concentrate according to claims 6 through 8, charac-
terized in that it contains as acid acetic acid, citric
acid, lactic acid, hydrochloric acid and/or an amino
acid.
- 15 10. A concentrate according to claims 6 through 9, charac-
terized in that it contains in the solution (B) addi-
tionally glucose, preferably 5 to 400 gs/l, especially
15 to 80 gs/l.
- 20 11. A concentrate according to claims 1 through 10, charac-
terized in that it contains the solution (A) in a
container which enables no or only a little escape of
CO₂ from the solution and the gaseous phase thereover.

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EUROPEAN SEARCH REPORT

Application number
EP 80 10 3136



European Patent
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EUROPEAN SEARCH REPORT

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Application number

EP 80 10 3136

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DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl. 7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	<u>US - A - 3 560 380 (STADE)</u> * Entirely * -----	1-11	
			TECHNICAL FIELDS SEARCHED (Int. Cl. 7)